## REMARKS/ARGUMENTS

Claims 31-34 are pending in the above-identified application. In view of the remarks set forth herein, reconsideration of all pending claims is respectfully requested.

### Double Patenting

The Examiner has rejected claims 31-34 under the judicially created doctrine of obviousness-type double patenting as follows:

Claims 31, 33, and 34 as allegedly unpatentable over claims 1, 3, 5, and 9 of U.S. Patent No. 5,885,971;

Claims 31-34 as allegedly unpatentable over claim 6 of U.S. patent No. 6,004,944;

Claims 31, 33, and 34 as allegedly unpatentable over claims 1, 2, 4, 7 and 8 of U.S. Patent No. 6,255,289; and

Claims 31-34 as allegedly unpatentable over claim 1 of U.S. patent No. 6,531,455.

Applicants agree to submit an appropriate terminal disclaimer upon an indication of otherwise allowable subject matter. The filing of a terminal disclaimer should not be construed as acquiescence in the rejection.

### Rejections under 35 U.S.C. § 103

Claims 31-33

Claims 31-33 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hickman *et al.* (*Human Gene Therapy* 5:1477-1483, 1994) (herein "Hickman") in view of Yang *et al.* (*Proc. Natl. Acad. Sci.* USA 90:4601-4605, 1993) (herein "Yang"). The Examiner states that Hickman teaches "gene delivery to the liver by direct injection of [a] naked DNA construct into the liver lobes ...," and that Hickman's naked DNA "comprises a sequence

encoding a secreted protein, human α-1-antitrypsin," which "is produced in the liver and appears in serum." The Examiner admits that Hickman does not teach intraductal delivery. Instead, the Examiner characterizes Yang as allegedly teaching that "intraductal delivery results in efficient gene expression into hepatocytes," and that "intraductal delivery of therapeutic genes to the liver may be applied to humans." Based on this characterization, the Examiner contends that Yang, which teaches intraductal delivery by a nonsurgical approach, provides a motivation to use the method of Hickman with intraductal delivery with a reasonable expectation of success. Applicants traverse the instant rejection as set forth below.

It is well-settled that a *prima facie* case under 35 U.S.C. § 103 requires a clear and particular showing, in the prior art, of a motivation sufficient to impel one to do specifically what applicant has done. *See* MPEP at §§ 2142 and 2143.01; *In re Fine*, 837 F.2d 1071, 5 USPQ2d at 1596, 1598, 1599 (Fed. Cir. 1988); *In re Dance,* 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). The suggestion or motivation to make the claimed combination must be found in the prior art and cannot be based on applicant's disclosure. MPEP § 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). *See also* MPEP §§ 2143 and 2143.01 (citing cases). Moreover, the proposed motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (Bd. Pat. App. Inter. 1993). The motivation must also be both objective and specific, *i.e.*, the Examiner's showing must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 50 U.S. P.Q.2d 1614, 1617 (Fed. Cir. 1999). It is this requirement for evidence of particularized motivation that provides a safeguard against the "tempting but forbidden zone of hindsight." *Id.* at 1616. Further, the cited art must be considered in its entirety, including portions that would teach away from the claimed invention. MPEP § 2141.02

In the present case, the cited art lacks any clear and particular motivation sufficient to impel the skilled artisan to achieve Applicants' invention. As set forth further below, Hickman and Yang discuss two different approaches for liver-directed gene expression, each approach targeting different cell types. When the teachings of these references are considered in their entirety, as required by the MPEP, the skilled artisan would not view the approach discussed in Yang as advantageous for modification of Hickman, particularly in the

context of naked DNA. If anything, Yang's intraductal delivery would be viewed as having disadvantages for achieving gene expression in hepatocytes as discussed in Hickman. Therefore, the skilled artisan would not look to Yang to modify the teachings of Hickman and, moreover, would view Yang as teaching away from the Examiner's proposed combination.

Hickman discusses a method for gene delivery targeting hepatocytes using plasmid DNA. (*See* Hickman at, *e.g.*, p. 1477 (Abstract & Overview Summary) and pp. 1480-1482 (Discussion).) Specifically, Hickman discusses direct injection of plasmid DNA encoding luciferase, β-galactosidase, or α-1-antitrypsin into liver and further describes the transfection of hepatocytes near the site of injection. (*See id.*, including Abstract and p. 1481, second col. last paragraph, bridging to p. 1481, first col.) In contrast, Yang, which is focused on treatment of cystic fibrosis (CF), discusses the specific, targeted delivery of recombinant adenoviruses to epithelial cells of the biliary tract. (*See* Yang at, *e.g.*, p. 4601 (Abstract) and p. 4602, second col., first full paragraph.) Yang points to the biliary epithelial cells as the primary target for treatment of CF via gene transfer, and specifically teaches away from other strategies that focus "exclusively on the hepatocyte as a target cell." (*Id.* at p. 4602, second col., first full paragraph.) As stated by Yang, the advantage of this approach "is the specificity of gene transfer achieved by virtue of the anatomical constraints of the compartment into which the virus is delivered; the primary target of gene transfer is the biliary epithelial cells, with recombinant gene expression detected in a minority of hepatocytes." (*Id.* at p. 4604.) Thus, because Yang discusses a method designed for selective targeting of biliary epithelial cells over hepatocytes, a skilled artisan reading Yang would not be impelled to use Yang's teachings to modify the method of Hickman, which, in contrast to Yang, is focused on targeting of hepatocytes.

In this regard, Applicants disagree with the Examiner's characterization of Yang's discussion *vis a vis* gene expression in hepatocytes. Contrary to the Examiner's view, Yang does not teach "efficient gene expression into hepatocytes" using intraductal delivery. As set forth above, Yang discusses targeted delivery of recombinant adenoviruses to the biliary tract. In determining the optimal dose of adenovirus for achieving gene expression in the biliary tract, it was shown that only the ***maximal*** dose of virus ($2 \times 10^{12}$ plaque-forming units (pfu)/ml) achieved any significant gene expression in hepatocytes. (*See id.* at p. 4603, first col., first full

paragraph (stating that the maximal concentration of virus "demonstrated *lacZ* expression in all of the biliary epithelial cells as well as >80% of the hepatocytes").) Using the next highest dose ($1 \times 10^{11}$ pfu/ml), recombinant gene transfer was observed in "<1% of all hepatocytes while *lacZ* expression was retained in all intrahepatic bile duct epithelial cells." (*Id.*) This discussion of an exceedingly rapid diminishment of gene transfer to hepatocytes, with delivery of submaximal doses of adenoviral vector to the biliary tract, does not support the Examiner's contention that Yang teaches "efficient gene expression into hepatocytes" using intraductal delivery. Indeed, in view of Yang's poor gene expression in hepatocytes observed with intraductally delivered adenovirus, and because introduction of adenoviral vectors is generally known to be a more efficient means for achieving gene expression that transfection with naked DNA, Applicants submit that the skilled artisan would view Yang as teaching away from the use of naked DNA for achieving efficient gene expression in hepatocytes by intraductal delivery.

Applicants also disagree with the Examiner's reliance on the assertion that Yang provides a motivation to modify Hickman because Yang teaches "that intraductal delivery is advantageous for human gene therapy." In particular, the Examiner contends that the asserted advantage stems from Yang's discussion that delivery can be achieved "by a nonsurgical approach, i.e., endoscopic retrograde cholangiography." Applicants again note, however, that Yang discusses the selective expression of transferred genes in the biliary epithelial cells versus hepatocytes, while Hickman is focused on achieving gene expression in hepatocytes. Thus, irrespective of any perceived advantage of a nonsurgical approach, the skilled artisan would not view Hickman as particularly amenable to modification according to Yang's approach, for reasons already discussed above. At the very least, any perceived advantage relating to a non-surgical aspect of intraductal delivery would be vastly outweighed by the perceived disadvantage of achieving markedly diminished, if any, gene expression in hepatocytes with naked DNA.

For at least the reasons above, the skilled artisan, reading Hickman and Yang and seeking to achieve efficient gene expression in hepatocytes, would not be motivated to use intraductal delivery of naked DNA in place of Hickman's approach of direct injection of into the liver. Withdrawal of the rejection is respectfully requested.

Claim 34

Claim 34 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hickman taken with Yang, as applied to claims 31-33, and further in view of Heartlein *et al.* (*Proc Natl. Acad. Sci. USA* 91:10967-10971, 1994) (herein "Heartlein"). Applicants traverse the instant rejection.

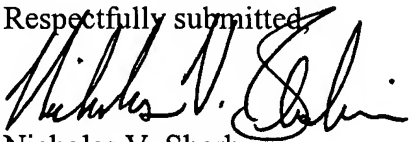
Heartlein discusses *in vivo* delivery of human growth hormone (hGH) by transplantation of genetically engineered primary fibroblasts expressing the hGH gene. (*See* Heartlein at, *e.g.*, p. 10967, second col., first full paragraph.) Heartlein, however, does not discuss intraductal delivery of DNA into a secretory gland and therefore does nothing to cure the deficiencies of Hickman and Yang as previously set forth above. Accordinlgy, for reasons discussed with respect to the rejection of claims 31-33 in view of Hickman and Yang, a *prima facie* case of obviousness has not been established with respect to claim 34. Withdrawal of the rejection is respectfully requested.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



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